

PATENT SPECIFICATION

(11) 1 200 159

1 200 159

NO DRAWINGS

- (21) Application No. 2091/70 (22) Filed 15 Aug. 1967
 (61) Patent of addition to No. 1,111,009 dated 14 April 1965
 (62) Divided out of No. 1,197,942
 (45) Complete Specification published 29 July 1970
 (51) International Classification A 61 k 21/00
 (52) Index at acceptance
 A5B 216 21Y



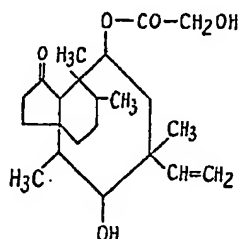
BEST AVAILABLE COPY

(54) VETERINARY ANTIBIOTIC COMPOSITIONS

(71) We, BIOCHEMIE KUNDL GMBH (Formerly Biochemie GmbH), an Austrian Company, of Kundl, Austria, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to water-soluble derivatives of pleuromutilin and veterinary antibiotics compositions useful in veterinary medicine.

Pleuromutilin is a known antibiotic and is of the formula,



The hydrogenation product of pleuromutilin is the above compound in which the vinyl group of pleuromutilin has been hydrogenated.

Our main patent specification Serial No. 1,111,009 describes and claims esters of pleuromutilin or its hydrogenation product which are formed by reaction of one or both of the hydroxy groups of pleuromutilin or its hydrogenation product with carbamate ester forming derivatives of isocyanic acid, with acylating derivatives of aliphatic monocarboxylic acids having from 3 to 19 carbon atoms or of haloformic or monohaloacetic acids, with acylating derivatives of aliphatic dicarboxylic acid having from 3 to 14 carbon atoms, or with sulphonylating derivatives of sulphonic acids.

In accordance with the present invention, there is provided a veterinary antibiotic composition incorporating as active ingredient a water-soluble ester of pleuromutilin or of its

hydrogenation product, or a water-soluble salt of a nester of pleuromutilin or of its hydrogenation product. The water-soluble salt may be obtained by reaction of a base with an ester of pleuromutilin or of its hydrogenation product having a free acid group, and the ester may be obtained by reaction of pleuromutilin or its hydrogenation product with an acid or an ester-forming derivative of an acid.

The water-soluble ester of pleuromutilin or of its hydrogenation product may comprise a water-soluble reaction product of pleuromutilin or its hydrogenation product and an ester-forming derivative of an acid selected from isocyanic acid, an aliphatic monocarboxylic acid having from 3 to 19 carbon atoms, a haloformic or monohaloacetic acid, an aliphatic dicarboxylic acid having from 3 to 14 carbon atoms, a mono-nuclear aromatic dicarboxylic acid, or a sulphonic acid.

As indicated in our main specification, the ester of the hydrogenation product of pleuromutilin may be obtained by reaction of the hydrogenation product of pleuromutilin with ester forming derivatives of the above-mentioned acids. Alternatively they may be prepared by hydrogenation of the esters after formation thereof. When the esters are subsequently reacted with a base to form a salt, hydrogenation may be carried out before or after reaction with a base. Hydrogenation of water-soluble ester of the invention may be carried out without destroying the water-solubility and activity of the esters.

The main specification describes various preferred classes of carbamate esters, carboxylate esters, and sulphonic acid esters. The active ingredient incorporated in the composition of the present invention may be such water-soluble esters, or water-soluble salts of such esters.

The physical-chemical characteristics of some particular water-soluble derivatives of pleuromutilin are described below. Such derivatives are suitable for use as active ingredient in the veterinary antibiotic composition of the present invention.

[Price 5s. 0d. (25p)]

1. Pleuromutilin succinate (free acid)

a) UV spectrum: little characteristic.

b) IR spectrum: Was taken in KBr and in CHCl_3 .The spectrum taken in CHCl_3 solution was used for characterisation.Interpretation of the spectrum in CHCl_3 (1% solution, thickness of layer 0.5 mm.):

Wave number (cm^{-1})	Band	Assigned to
3500	blurred	—OH ass.
3000—2860	clear	—CH ₃ , —CH ₂ —
2700—2500	hinted	—COOH
1740	clear	carbonyl function (super position of $>\text{C}=\text{O}$, —COOR, —COOH)
1450, 1380	clear	presumably CH— oscillations
1150	clear	(probably CO) (super- position)
1115	clear	—OH sec.
1010	clear	C—O valency oscillation

c) Equivalent weight: theoretical 478
 found 469

2. Pleuromutilin glutarate (free acid)

a) UV spectrum: little characteristic

b) IR spectrum: essentially identical with that of Pleuromutilin succinate.

Variations: in the range 1500—1360 cm^{-1} inflection at 1460, small band at 1410 cm^{-1} .

c) Equivalent weight: theoretical 492
 found 484

BEST AVAILABLE COPY

3. Pleuromutilin phthalate (free acid)

a) UV spectrum: little characteristic.

b) IV spectrum:

Wave number (cm^{-1})	Band	Assigned to
3680	quite clear	—OH valency oscillation?
3500	blurred	—OH ass.
3000—2860	clear	—CH ₃ , —CH ₂ —
2700—1500	hinted	—COOH
2000—1800	hinted	aromat.
1740	clear	carbonyl function (super- position of CO, —COOR, —COOH)
1600, 1580	clear	aromat.
1450, 1375	clear	presumably CH— oscillations
1115	clear	—OH sec.
1080	clear	aromat.?
1010	clear	C—O—valency oscillation

c) Equivalent weight: theoretical 526
found 514

4. N-carboxymethylcarbonyl derivative of Pleuromutilin (free acid)IR spectrum: taken in CHCl_3 (1% solution, thickness of layer 0.5 mm)

Wave number (cm^{-1})	Band	Assigned to
3440	clear	—CONHR—
3000—2870	clear	—CH ₃ , —CH ₂ —
2700—2500	hinted	—COOH
1730	clear	superposition of the individual carbonyl functions
1605	clear	presumably —NHR— deformation oscillation
1500	clear	source unknown
1120	clear	presumably —OH sec.

5. N-(α -carboxyethyl)-carbamoyl derivative of Pleuromutilin (free acid)

IR spectrum:

Wave number (cm^{-1})	Band	Assigned to
3435	clear	—CONHR—
3000—2870	clear	—CH ₃ , —CH ₂ —
2700—2500	hinted	—COOH—
1730	clear	superposition of the individual carbonyl functions
1600	clear	presumably —NHR— deformation oscillation
1500	clear	source unknown
1120	blurred	presumably —OH sec.

6. N-(α -carboxybenzyl)-carbamoyl derivative of Pleuromutilin (free acid)

IR spectrum:

Wave number (cm^{-1})	Band	Assigned to
3430	clear	—CONHR—
3000—2870	clear	—CH ₃ , —CH ₂ —
2700—2500	hinted	—COOH
1730	clear	superposition of the individual carbonyl functions
1605	clear	presumably —NHR— deformation oscillation
1495	clear	source unknown
1115	clear	presumably —OH sec.

Spectrum taken in KBr (1.5 mg/300 mg):

Wave number	Band	Assigned
720, 700	clear	monosubstituted aromatic

The UV spectra were taken in absolute alcohol with a Zeiss spectrophotometer RPQ 20 AV.

5 The IR spectra were taken with a Perkin-Elmer apparatus 237.

10 The pleuromutilin derivatives exhibit an effect chiefly directed against gram-positive germs (staphylococci, streptococci). Various microorganisms, e.g. staphylococci, which have

become resistant to penicillin and other antibiotics react to pleuromutilin in a manner analogous to the staphylococci which are sensitive to penicillin. A very good effect against gram-negative microorganisms is also observed in the case of the *Shigella-flexneri* group. The pleuromutilin derivatives are also indicated for use in treating illnesses produced by PPLO (pleuropneumonia-like organisms) in different

animals species (mycoplasmas) and illnesses caused in different animals by coccidia and worm invasions.

- 5 The water-soluble derivatives of pleuromutilin are antibiotically useful in therapy in that they are easily taken up in the blood stream. Injectable solutions may be prepared from the water-soluble derivatives. A particular antibiotic use of the water-soluble derivatives of pleuromutilin is the treatment of dog's acne which is very resistant to antibiotics. The derivatives are also useful against the germs produced by secondary distemper.

WHAT WE CLAIM IS:—

- 15 1. A veterinary antibiotic composition incorporating as active ingredient a water-soluble ester of pleuromutilin or of its hydrogenation product, or a water-soluble salt of an ester of pleuromutilin or of its hydrogenation product.

- 20 2. A veterinary antibiotic composition according to claim 1 in which the water-

soluble salt of an ester of pleuromutilin or its hydrogenation product is produced by reaction of a base with an ester of pleuromutilin or of its hydrogenation product having a free acid group. 25

3. A veterinary antibiotic composition according to claim 1 or claim 2 in which the ester of pleuromutilin or of its hydrogenation product is obtained by reaction of pleuromutilin or its hydrogenation product with an acid or an ester forming derivative of an acid. 30

4. A veterinary antibiotic composition incorporating as active ingredient a water-soluble derivative of pleuromutilin substantially as herein described. 35

MATHYS & SQUIRE,
Chartered Patent Agents,
10 Fleet Street,
London, E.C.4.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

BEST AVAILABLE COPY